Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement†

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Background. We compared analgesia after intrathecal sufentanil alone, sufentanil with epinephrine 200 μg and sufentanil with clonidine 30 μg in patients after total hip replacement, the endpoints being onset and duration of action.

Methods. We performed a randomized double-blind study of 45 patients for elective total hip arthroplasty using continuous spinal anaesthesia. As soon as a pain score higher than 3 on a 10 cm visual analogue scale was reported, sufentanil 7.5 μg alone, sufentanil 7.5 μg + epinephrine 200 μg or sufentanil 7.5 μg + clonidine 30 μg in 2 ml normal saline was given intrathecally. Pain scores, rescue analgesia (diclofenac and morphine) and adverse effects (respiratory depression, postoperative nausea and vomiting, itching) were observed for 24 h after surgery.

Results. Time to a pain score of <3 [6 (SD 1) *vs* 6 (1) *vs* 5 (1) min], time to the lowest pain score [7 (2) *vs* 8 (2) *vs* 8 (2) min] and time to the first dose of systemic analgesic for a pain score >3 [281 (36) *vs* 288 (23) *vs* 305 (30) min] were similar in all three groups. Adverse effects and analgesic requirements during the first 24 h were also similar.

Conclusion. After total hip replacement, all three analgesic regimens gave good analgesia with comparable onset and duration of action, and minor adverse effects.

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Intrathecal (i.t.) opioid analgesia is widely used in labour[1 2] and is also used after general surgery.[3 4] Spinal lipophilic opioids, such as fentanyl, sufentanil and nalbuphine,[4 5] give prompt and profound analgesia compared with the slow onset of action of i.t. morphine.[5] I.T. sufentanil provides nearly instantaneous pain relief, but its duration of action is relatively short in labour (60–90 min),[6 7] whereas the analgesic effect is longer when this opioid is administered for postoperative pain relief after total hip replacement (240 min).[4]

A longer duration of analgesia after i.t. sufentanil would be useful for patients undergoing orthopaedic surgery. A longer action might be obtained by adding either epinephrine or clonidine, as found in obstetrics, in which epinephrine (200 μg)[2] and clonidine (30 μg)[10] mixed with sufentanil significantly prolong analgesia.

In this double-blind, randomized study we compared the speed of onset and duration of action after i.t. administration of sufentanil 7.5 μg alone and mixed with either epinephrine 200 μg or clonidine 30 μg for postoperative pain relief in elderly patients undergoing total hip arthroplasty.

Methods

After obtaining institutional ethics committee approval and informed consent, we studied 45 patients aged more than 70 yr, ASA physical status II–IV, scheduled for elective total hip replacement. We excluded patients with psychiatric illness, allergy to opiates, the study drugs or local anaesthetics, severe chronic obstructive respiratory disease (forced expiratory volume in 1 s <600 ml) or coagulation disorders. On the basis of previous studies,[1 4 8] we expected analgesia to be prolonged for 60 min, giving a standardized difference of 1.3. To detect a prolongation in duration of

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Table 1 Patient characteristics [mean (SD or range), n=15 for each group]. ASA, American Society of Anesthesiologists; SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF	SUF + EPI	SUF+CLO
Age (yr)	76 (70–82)	79 (73–85)	78 (71–85)
Height (cm)	167 (8)	163 (10)	166 (8)
Weight (kg)	75 (11)	71 (15)	78 (15)
Females, males	5, 10	10, 5	6, 9
ASA class 2, 3, 4	3, 12, 0	5, 10, 0	4, 11, 0

60 min, 15 patients per group would be needed for β=0.2 and α=0.05.

All patients were given morphine 0.1 mg kg^{-1} s.c. 60 min before the operation, to obviate opioid supplements. These can be needed during surgery because of the prolonged lateral decubitus position, which sometimes causes shoulder pain. In the operating room, an i.v. infusion of lactated Ringer solution was started through a 17 gauge peripheral venous catheter. Electrocardiogram, non-invasive arterial blood pressure and peripheral oxygen saturation were measured and a urinary catheter was inserted. Continuous spinal anaesthesia was administered with the patient in the lateral position, operation side up, at the L2–3 or L3–4 intervertebral space using an 18 gauge Tuohy needle (epidural miniset), and a 20 gauge catheter was inserted 3–4 cm into the subarachnoid space. Injections of 0.5% isobaric bupivacaine 2.5 or 5 mg (Carbostesine®, Astra, Dietikon, Switzerland) were given as required. Surgery was performed to a standard plan.

After surgery, the i.t. catheter was flushed with normal saline 2 ml and left in place. Patients received oxygen by face mask. In the recovery room, when the pain score on the operated side was greater than 3/10 on a visual analogue scale (VAS; 0=no pain at all, 10=unbearable pain), the patients were randomly allocated (by the closed envelope technique) to one of the three study groups: group SUF received sufentanil 7.5 μg (Sufenta®, Janssen-Cilaf, Baar, Switzerland) alone, group SUF+EPI received sufentanil 7.5 μg with epinephrine 200 μg, and group SUF+CLO received sufentanil 7.5 μg with clonidine 30 μg, all in normal saline 2 ml through the i.t. catheter over 30 s. Study drugs were prepared by an anaesthetist who was the only person with access to the randomization list and was not otherwise involved in the study. The first author (RF) injected drugs blindly and tested the patients during the first hour. Afterwards, the patients were tested by the nurse in charge and, after leaving the recovery room, by ward nurses, who collected the data and gave the analgesics according to the study plan. Twenty-four hours after the i.t. opioid injection, one of the authors (RF or ZG) collated the data.

Pain score, sedation score (1=awake and alert; 2=awake but drowsy, responding to a verbal stimulus; 3=drowsy but rousable, responding to a physical stimulus; 4=unrousable, not responding to a physical stimulus), respiratory rate, oxygen saturation and haemodynamic changes were measured at i.t. injection and then every 2.5 min for the first 15 min, every 5 min for the next 45 min and every hour for the next 5 h. We noted times to VAS <3 (onset of action), to the lowest VAS and to the first systemic analgesic intervention (reappearance of hip pain, VAS >3) and recorded ketorolac (Toradol®, Roche, Reinach, Switzerland) and morphine requirements (rescue analgesia given by the systemic route) during the first 24 h after i.t. injection. We recorded side-effects of nausea and/or vomiting, pruritus (grade 1=mild, not disturbing; grade 2=moderate, disturbing but not requiring treatment; grade 3=severe, requiring treatment) and respiratory depression (respiratory rate < 8/min).

Patients could request systemic rescue analgesia if their pain score was still greater than 3/10 30 min after i.t. injection or after the i.t. analgesia regressed. Ketorolac 30 mg i.v. was available first, followed by morphine 0.1 mg kg^{-1} s.c. if the VAS was still greater than 3/10 after 30 min. Afterwards, these analgesics were given on demand (pain score >3) with a maximum of three doses per 24 h for ketorolac and eight doses per 24 h for morphine.

Nausea and/or vomiting were treated with metoclopramide (Primperan®, Synthélabo, Lausanne, Switzerland) 10 mg i.v. and a reduction in mean arterial blood pressure (MAP) by more than 20% of resting value with ephedrine 5 mg i.v. and a rapid infusion of normal saline 250 ml. Clemastine (Tavegil®, Novartis, Bern, Switzerland) 2 mg i.v. was administered for severe pruritus and naloxone (Narcan®, Dupont Pharma, Bad Homburg, Germany) 40 μg i.v. was injected for respiratory depression (respiratory rate <8 b.p.m.). The patients only left the recovery room for the ward after receiving the first rescue analgesia.

Statistical analysis

Data are presented as mean (SD) or median (range) and groups were compared by analysis of variance or the Kruskal–Wallis test as required; a P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics, presented in Table 1, were comparable between groups. No supplementary i.v. opiates or sedatives were administered during surgery.

Pain scores, onset and duration of action of i.t. sufentanil alone and with epinephrine or clonidine are presented in Table 2 and Figures 1 and 2. Results were comparable in the three groups. After i.t. injection, all patients achieved a VAS of 0 (Table 2).

Although a slightly shorter onset and longer duration of action was observed with the sufentanil–clonidine mixture, the differences were not statistically significant (Figs 1 and 2).

Table 2 Pain scores (10-point VAS scale), onset and duration of action in the three groups [mean (SD) or median (range), *n*=15 for each group]. SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF	SUF+EPI	SUF+CLO
Pain score before injection	5 (4–8)	5 (4–10)	5 (4–9)
Time to pain score <3 (min)	6 (1)	6 (1)	5 (1)
Time to lowest pain score (min)	7 (2)	8 (2)	8 (2)
Time to first systemic analgesic intervention (min)	281 (36)	288 (23)	305 (30)
Lowest pain score	0	0	0
Pain score at 24 h	0 (0–1)	0 (0–2)	0 (0–2)

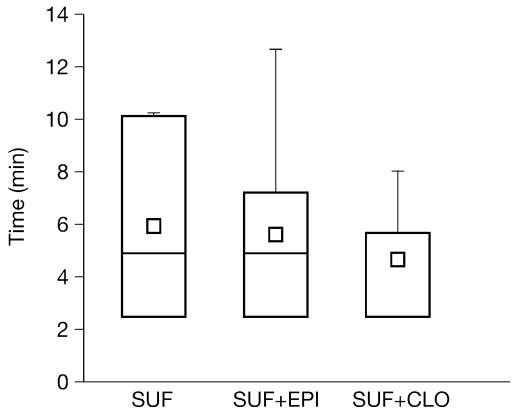

Fig 1 Box plots showing the onset of action (time between initial intrathecal injection and reaching pain score <3) in all groups. Open boxes represent the 25th to 75th percentiles and contain the median (horizontal bar) and mean (small square) values; vertical bars represent the 10th to 90th percentiles.

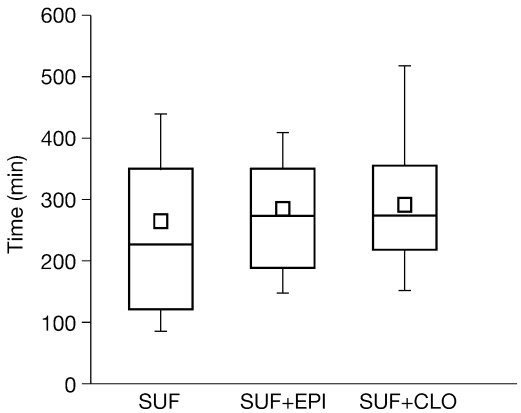

Fig 2 Box plots showing the duration of action [time from initial intrathecal injection to reappearance of a pain score (VAS) of >3, requiring the first systemic analgesic intervention] in all groups. Open boxes represent the 25th to 75th percentiles and contain the median (horizontal bar) and mean (small square) values; vertical bars represent the 10th to 90th percentiles.

The analgesic requirements in the first 24 h were similar (Table 3). One patient in the SUF group, two in the SUF+EPI group and two in the SUF+CLO group were not considered for analysis of postoperative analgesic requirements because they received further i.t. analgesia.

The cardiovascular changes in the first hour after i.t. injection were comparable in all groups (Table 4). Ephedrine was given to one patient in the SUF group, two patients in the SUF+EPI group and four patients in the SUF+CLO group.

Respiratory rates less than 8 b.p.m. were not seen. However, one patient in the SUF+EPI group had an oxygen saturation less than 95% for a short time, requiring adjustment of oxygen administration. Four patients in the SUF group, six in the SUF+EPI group and eight in the SUF+CLO group complained of pruritus in the first hour after i.t. injection. Antihistamines were required in two patients in each of the SUF and SUF+EPI groups and in one patient in the SUF+CLO group. Before rescue analgesia, two patients in the SUF group, four in the SUF+EPI group and one in the SUF+CLO group had nausea and/or vomiting requiring antiemetic therapy. Sedation score never exceeded grade 2 in any patients in the first hour after i.t. injection.

Discussion

We believe this is the first study of analgesia from sufentanil–epinephrine and sufentanil–clonidine combinations for postoperative pain relief in patients, apart from obstetrics. All the treatment gave, within 5–6 min, excellent pain relief which lasted for 4.5–5 h. No significant differences between groups were found in the quality of pain relief assessed by VAS pain scores, onset or duration of analgesic action, adverse effects and subsequent analgesic treatment.

We added epinephrine 200 μg to sufentanil, as this dose is commonly used in obstetrics without circulatory effects.[2 6 8] Cardiovascular effects of i.t. clonidine are a serious concern, and in our frail, elderly patients we gave a moderate dose of 30 μg, which seems to prolong the analgesic action of i.t. sufentanil in labour and to have acceptable effects on the circulation.[1]

The prolongation of analgesia by epinephrine has in the past been attributed to vasoconstriction, reducing the clearance of coadministered drugs from the subarachnoid space.[9] However, epinephrine does not reduce the maximal plasma concentration of local anaesthetics.[10 11] An alternative explanation for the prolongation of spinal anaesthesia by vasoconstrictors may be a direct effect on the nociceptive system in the dorsal horn of the spinal cord,[12] where opioids and adrenergic agonists may interact. In cats, the suppression of nociception by fentanyl is increased by epinephrine.[12] In humans, the effects of epinephrine in addition to i.t. sufentanil, which have been only described in labour, are controversial. A study[8] of sufentanil 10 μg i.t. with or without epinephrine 200 μg reported a significant but small prolongation of analgesia from 115 to 132 min, and another

Table 3 Analgesic requirements during the first 24 h after intrathecal injection [mean (SD) or median (range)]. SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF (*n*=14)	SUF+EPI (*n*=13)	SUF+CLO (*n*=13)
Ketorolac (mg/patient)	30 (23)	37 (29)	33 (20)
Morphine (mg/patient)	11.5 (6)	13(11)	16 (10)
Number of analgesic doses/patient	2.5 (1–5)	3 (1–6)	3 (1–6)

Table 4 Changes in mean arterial pressure (MAP) and heart rate during the first hour after intrathecal injection [mean (SD), *n*=15 in each group]. SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF	SUF+EPI	SUF+CLO
Baseline MAP (mm Hg)	93 (19)	90 (20)	97 (12)
Maximal decrease in MAP (%)	14 (10)	22 (18)	23 (9)
Time to maximal decrease in MAP (min)	20 (19)	21 (18)	23 (14)
Baseline heart rate (beats min^{-1})	74 (17)	76 (16)	76 (17)
Maximal decrease in heart rate (%)	7 (8)	9 (11)	8 (8)
Time to maximal decrease in heart rate (min)	16 (16)	16 (15)	25 (18)
Ephedrine (number of patients)	1	2	4

showed pain relief for 90 min in both groups.[6] Our data support this finding. Two other studies in labour suggest a more pronounced effect of epinephrine added to a mixture of bupivacaine and sufentanil. Gautier and colleagues[13] found that a small dose of epinephrine (25 μg) added to bupivacaine 1 mg and sufentanil 5 μg i.t. prolonged the analgesia by about 40 min. Campbell and colleagues[2] added a larger dose of epinephrine 200 μg to sufentanil 10 μg and bupivacaine 2.5 mg, and reported a prolongation of 43 min. Adding epinephrine to a mixture of local anaesthetic and opioids seems more efficient in prolonging analgesia than adding it to sufentanil alone, and the reason for this is not clear.

We found only a trend to prolongation of pain relief in the SUF+CLO group compared with the control SUF group (305 *vs* 281 min), whereas the addition of clonidine 30 μg to sufentanil 5 μg prolonged labour analgesia from 99 to 145 min[1] and from 97 to 125 min.[14] These differences may be related to the different type of pain, with an increasing and changing pattern during labour (somatic to visceral) compared with postoperative pain, which tends to decrease with time. Compared with labour analgesia, the pain relief in our elderly patients lasted 281 (36) min and the addition of clonidine 30 μg was probably not enough to improve the analgesia provided by sufentanil 7.5 μg alone. A larger dose of clonidine, e.g. 50 μg, might have provided a longer duration of pain relief, as demonstrated by d'Angelo and colleagues,[15] who found labour analgesia lasting 197 min after adding clonidine 50 μg to sufentanil 7.5 μg and bupivacaine 2.5 mg, and 132 min for sufentanil–-bupivacaine.

Clonidine extends labour analgesia when added to i.t. opioids, but causes hypotension.[1 13 14 16 17] The incidence of hypotension was doubled by adding clonidine 30 μg to sufentanil 5 μg (25 *vs* 50%).[1] Mercier and colleagues found that 63% of patients developed hypotension with the same analgesic regimen.[14] Sia reported a decrease in blood pressure in 60% of parturients receiving bupivacaine 1.25 mg, sufentanil 5 μg and clonidine 30 μg compared with only 7% in a control group without clonidine.[16] We found a maximal decrease in MAP, from the baseline value, of 22 and 23% in the SUF+EPI and SUF+CLO groups respectively, compared with 14% in the SUF control group (Table 4). The trend towards greater hypotension in the SUF+CLO group is not surprising,[1 14] but a 22% decrease in blood pressure after adding epinephrine has not been described previously. Apart from profound analgesia reducing sympathetic activity, no other explanation is evident. The number of patients in this study may have been insufficient to detect other cardiovascular effects.

Pruritus was noted in 40% (18 out of 45 patients), with no differences between the groups. Severe itching requiring antihistamines occurred in five patients (11%).

These data are consistent with our previous report[4] and well below the 80–100% observed in obstetric studies.[1 2] Pregnant women may be more susceptible than elderly patients, possibly for hormonal reasons. Epinephrine did not decrease the incidence of pruritus in our patients, contrary to Camman and colleagues' study, in which pruritus was reduced by 50% in the epinephrine group.[6]

Postoperative nausea and/or vomiting was not statistically different between groups. We found no greater incidence in the SUF+EPI group, in contrast to the finding of Camman and colleagues (0% without epinephrine *vs* 35% with epinephrine).[6]

In conclusion, after total hip replacement, i.t. sufentanil alone or mixed with epinephrine or clonidine provides excellent analgesia (a pain score of 0 was achieved in all patients investigated), with comparable onset and duration of action. Clonidine and epinephrine tend to decrease blood pressure, so we do not recommend adding these agents to sufentanil.

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